

DAIDS	Appendix 2	No.: DWD-POL-LB-01.00A2
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DAIDS Requirements for Non-US Laboratories Guidance to Investigators Applying for Funding to Conduct HIV/AIDS Clinical Trials

This document outlines the DAIDS laboratory-related requirements and deliverables to be included in a Comprehensive Laboratory Plan.

1.0 Diagnosis, safety tests, CD4 and Virological tests, and Primary endpoints

Tests that are used for diagnosis of infection (e.g., HIV, TB, Syphilis, HSV), determining eligibility (e.g., pregnancy test), monitoring the safety of the intervention (e.g. hematology, chemistry), making patient management decisions (e.g., CD4, viral load), or as primary study endpoints must be performed in laboratories that are conducting operations in a Good Clinical Laboratory Practices (GCLP) manner. Tests must be quality assured by external proficiency testing surveys provided by the College of American Pathologists (CAP) or equivalent, and the use of FDA (or equivalent)-approved methodologies is strongly encouraged. If non-approved methods are considered, these must be validated in a study that compares a proposed methods to a FDA (or equivalent)-approved one. Guidelines for conducting a validation study are described in the Method Validation document:

<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/labs/MethodValidation.pdf>

The elements of GCLP are described in the Good Clinical Laboratory Practices document:

<http://www3.niaid.nih.gov/NR/rdonlyres/6837341A-D644-4D40-A0F0-E66995201B45/0/ElementsOfGCLP.doc>

The training of laboratory staff in the principles of GCLP is strongly encouraged. For information about DAIDS-sponsored GCLP training workshops, please contact Janice Darden at jdarden@niaid.nih.gov.

Accreditation by CLIA (<http://www.cms.hhs.gov/clia/>) or an equivalent in-country organization, e.g., SANAS (<http://www.sanas.co.za/>) is highly recommended.

A. CD4 testing

CD4 determinations must be done using standard flow cytometric measurements, and consideration should be given to CDC guidelines that describe dual-platform technology - MMWR 1997;46 [No. RR-2,

<http://www.cdc.gov/mmwr/preview/mmwrhtml/00045580.htm> or single-platform technology - MMWR 2003;52(RR-2),

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5202a1.htm>.

The CD4 laboratory must successfully participate in the CD4 proficiency testing (PT) program administered by the UK NEQAS and must be responsive to the trouble-shooting and assistance efforts by the DAIDS Immunology Quality Assessment (IQA) contract. Information about the UK NEQAS CD4 PT program can be found at www.ukneqasli.org. Enrollment in this program will have to be requested from DAIDS. Please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov. Proficiency testing samples are

sent every two months, beginning with January. The CD4 laboratory will have to pass at least one round of PT before testing study subjects.

Annual cost of participation is approximately \$400 (US) when all forms and results are returned by the web, and approximately \$450 (US) if returned by mail or fax. There is an additional \$130 (US) annual cost for shipping the PT samples from the UK NEQAS to the laboratory by courier (TNT/DHL). These costs should be taken into account when preparing the budget for conducting the study. There is no fee for receiving assistance from the DAIDS IQA.

B. HIV Virology

The use of FDA-approved methods is strongly encouraged.

Consensus virological methods can be found at: <http://aactg.s-3.com/labmanual.htm>.

Laboratories performing HIV RNA PCR, HIV DNA PCR and resistance testing must participate in the DAIDS Virology Quality Assurance (VQA) program. More information about this program may be found at: <http://aactg.s-3.com/vqa.htm>.

To request enrollment in VQA PT program(s), please contact Joe Fitzgibbon at 301 451 2738 or email to jfitzgibbon@niaid.nih.gov. For HIV viral load certification, the laboratory is required to successfully complete testing of an initial panel of 20 coded samples and two subsequent five-sample panels. The process of achieving certification takes at least five months.

There is no fee for participating in this program.

C. Other tests

Tests must be monitored by external proficiency testing (PT) surveys provided by the College of American Pathologists (CAP) or equivalent. Non-CAP providers of proficiency testing panels must be reviewed and approved by DAIDS.

To check on the suitability of non-CAP proficiency testing providers, please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov.

Different providers of PT surveys send samples at different frequencies. Most CAP surveys are sent three times a year. The laboratory will have to successfully pass at least one round of PT for each test. PT results (raw data) will have to be sent to a DAIDS contractor – SMILE (patient Safety Monitoring in International Laboratories) - for review. The laboratory will receive assistance and instructions for corrective actions from SMILE. For instructions to submit PT results please contact Daniella Livnat at 301 435 3775 or email to dlivnat@niaid.nih.gov.

The laboratory will have to successfully complete two rounds of proficiency testing before testing study subjects.

The cost of participation in proficiency testing programs should be taken into account when preparing the budget for conducting the study.

DAIDS will verify participation and successful performance of the laboratory in the various proficiency testing programs.

For requirements described in Section I above, please include the following in the Comprehensive Laboratory Plan:

- Proof of laboratory accreditation if available
- A spreadsheet that lists all the tests that will be done for the study, all the laboratories in which these tests will be done, and the external QA providers and proficiency testing surveys that will be used to monitor each test. The template below is provided for your convenience as an example of how this information can be provided. You may modify this as appropriate.
<http://www3.niaid.nih.gov/NR/rdonlyres/C1076997-2029-42B5-AC25-39E53E8C4686/0/LabSpreadsheet.xls>
- A completed Laboratory Self-Description Module for each proposed participating laboratory. The template below is provided for your convenience as example of how this information can be provided. You may modify this as appropriate.
<http://www3.niaid.nih.gov/NR/rdonlyres/474B75F3-D526-4C0E-BE8F-086A87C34B55/0/LabSelfDescModule.doc>
- Proof of accreditation/certification or equivalent for each laboratory if available
- Normal ranges for tests or a plan to obtain normal ranges by testing specimens from the local population
- For each participating laboratory, provide the following Standard Operating Procedures (SOPs). (The attached documents provide the elements that should be included in the SOPs):
 - tests to be employed in the study in a format that includes information about test principle, specimen requirements, reagents, supplies and equipment, procedure, calculations, quality control, procedural notes and references
 - Bio-Safety (biohazard, occupational, chemical):
<http://www3.niaid.nih.gov/NR/rdonlyres/BD30CC5A-9FC7-4962-9AE0-48DC88D1E3EC/0/ChemBiohazardSOPElements.doc>
 - Instrument operation, calibration, maintenance and validation:
<http://www3.niaid.nih.gov/NR/rdonlyres/6CF731F6-629A-460D-94FF-A3172D4DC778/0/EquipmentSOPElements.doc>
 - General specimen management (collection, receipt, processing, testing, shipping and tracking):
<http://www3.niaid.nih.gov/NR/rdonlyres/4696CACF-7A99-45D3-A436-B3A345D6FBCE/0/SpecimenMgmtSOPElements.doc>
 - General data management (description of computerized systems, data acquisition, recording/entry, modification, signatures, export, archiving, security, and integration into the study database):
<http://www3.niaid.nih.gov/NR/rdonlyres/8A5F0FBE-5FBE-49A1-B251-8E84B128F0FE/0/LabDataMgmtSOPElements.doc>

DAIDS will verify participation and successful performance of the laboratory in the various proficiency testing programs

2.0 Research Use Only endpoint tests (research tests not yet validated and approved by an ICH regulatory body such as the FDA)

Research Use Only endpoint tests (e.g., ELISPOT, ICC, pharmacological, virological) should be performed in laboratories that conduct operations in a Good Clinical Laboratory Practices (GCLP) manner. External proficiency testing should be applied to such tests. If existing proficiency testing surveys are not available, a suitable form of alternative proficiency assessments needs to be devised and proposed.

A description of the elements of GCLP and a comprehensive presentation about GCLP are found in section I above. The training of laboratory staff in the principles of GCLP is strongly encouraged. For information about DAIDS-sponsored GCLP training workshops, please contact Janice Darden at jdarden@niaid.nih.gov.

For requirements described in Section II above, please include the following in the Comprehensive Laboratory Plan:

- A list of the RUO tests
- Test SOPs in a format that includes information about test principle, specimen requirements, reagents, supplies and equipment, procedure, calculations, quality control, procedural notes and references
- Complete identifying information for the laboratories indicated above
- A description of the external proficiency testing measures undertaken for each test in each laboratory
- A documentation of the ability of staff to proficiently perform proposed tests
- A description of the GCLP operations in the laboratory

3.0 Study-specific Specimen Management plan

Each study must have a specimen management plan that describes sample acquisition, recording, testing, storing and shipping, including specimen flow chart, QA oversight and corrective action (the latter two may be included in the Laboratory QA plan). If shipments of specimens are to occur, they must be done according to the most current International Air Transport Association (IATA) shipping regulations:

<http://www.iata.org/ps/publications/9065.htm>.

For requirements described in Section III above, please include the following in the Comprehensive Laboratory Plan:

- The specimen management plan
- Proof of training in IATA shipping regulations (certification) if specimen shipments are planned for the study

4.0 Study-specific Laboratory Data Management plan

Each study must include a laboratory data management plan that describes the systems and processes for acquisition, data entry, recording, exporting, reporting, modification, security and archiving of laboratory test results. The plan should describe the QA oversight and corrective actions, and how all laboratory test results will be integrated into the general study database. If the laboratory plans to use a Laboratory Information Management System (LIMS) or a Laboratory Data Management System (LDMS), the elements of 21 CFR part 11 compliant (http://www.fda.gov/ora/compliance_ref/part11/) should be taken into consideration.

For requirements described in Section IV above, please include the following in the Comprehensive Laboratory Plan:

- The laboratory data management plan
- A description of the testing that was done to ensure that data flow smoothly and maintain integrity from the point of acquisition to the study database
- Proof of 21 CFR part 11 compliance if available

5.0 Laboratory QA plan

The study must have a laboratory quality assurance plan to regularly review all components of laboratory activities, including intervention and corrective action plan, and plans for backup testing facilities. The Elements of the laboratory QA Plan are described in the attached document: <http://www3.niaid.nih.gov/NR/rdonlyres/6AFF42D5-58BB-4A79-BF52-78AE156FEB2C/0/ElementsOfQMPlan.doc>

For requirements described in Section V above, please include the following in the Comprehensive Laboratory Plan:

- The laboratory QA plan

6.0 Laboratory-specific auditing - provided by DAIDS

DAIDS and/or its contractors will conduct laboratory-specific audit visits to determine laboratory readiness to participate in trials, and, as indicated, during the conduct of a trial. The Laboratory Assessment document shows the scope of the audit: <http://www3.niaid.nih.gov/NR/rdonlyres/C012BE9C-88EC-476A-89D5-4338ED612748/0/DAIDSLabAudit.doc>